GENE SIGNATURES PREDICTIVE OF METASTATIC DISEASE

FIELD OF THE INVENTION

[0001] The present invention relates to cancer and in particular to prostate cancer and ER positive breast cancer. Provided are methods for characterising and prognosing cancer and in particular prostate cancer and ER positive breast cancer. The methods utilize various biomarkers, specifically in the form of one or more gene signatures. Primers, probes, antibodies, kits, devices and systems useful in the methods are also described.

BACKGROUND OF THE INVENTION

[0002] Prostate cancer is the most common malignancy in men with a lifetime incidence of 15.3% (Howlader 2012). Based upon data from 1999-2006 approximately 80% of prostate cancer patients present with early disease clinically confined to the prostate (Altekruse et al 2010) of which around 65% are cured by surgical resection or radiotherapy (Kattan et al 1999, Pound et al 1999). 35% will develop PSA recurrence of which approximately 35% will develop local or metastatic recurrence, which is non-curable. At present it is unclear which patients with early prostate cancer are likely to develop recurrence and may benefit from more intensive therapies. Current prognostic factors such as tumour grade as measured by Gleason score have prognostic value but a significant number of those considered lower grade (7 or less) still recur and a proportion of higher-grade tumours do not. Additionally there is significant heterogeneity in the prognosis of Gleason 7 tumours (Makarov et al 2002, Rasiah et al 2003). Furthermore it has become evident that the grading of Gleason score has changed leading to changes in the distribution of Gleason scores over time (Albertsen et al 2005, Smith et al 2002).

[0003] It is now clear that most solid tumours originating from the same anatomical site represent a number of distinct entities at a molecular level (Perou et al 2000). DNA microarray platforms allow the analysis of tens of thousands of transcripts simultaneously from archived paraffin embedded tissues and are ideally suited for the identification of molecular subgroups. This kind of approach has identified primary cancers with metastatic potential in solid tumours such as breast (van 't Veer et al 2002) and colon cancer (Bertucci et al 2004).

DESCRIPTION OF THE INVENTION

[0004] The present invention is based upon the identification and verification of cancer biomarkers, particularly prognostic biomarkers that identify potentially metastatic cancers (such as prostate and ER positive breast cancers).

[0005] The present inventors have identified a group of primary prostate cancers that are similar to metastatic disease at a molecular level. Primary tumour samples which clustered with metastatic samples define a group with poor (bad) prognosis. These tumours may be defined by down regulation of genes associated with cell adhesion, cell differentiation and cell development. These tumours may be defined by up regulation of androgen related processes and epithelial to mesenchymal transition (EMT). In contrast, benign and primary like benign tumours cluster to define a group with improved (good) prognosis. A series of biomarker/gene signatures that can be used to prospectively identify tumours within either subgroup (i.e. with metastatic or non-metastatic biology) have been generated and validated which have prognostic power. The signatures can thus be used to prospectively assess a tumour's progression, for example to determine whether a tumour is at increased likelihood of recurrence and/or metastatic development. The signatures also display excellent performance in heterogeneity studies as discussed further herein. In particular, a 70 gene signature is described herein. The gene signatures are also shown to be effective in other cancer types including ER positive breast cancer, thus suggesting that the underlying molecular biology may have applicability in defining potentially metastatic primary tumours.

[0006] Thus, in a first aspect the invention provides a method for characterising and/or prognosing cancer, such as prostate cancer or ER positive breast cancer, in a subject comprising: determining the expression level of at least one gene from Table 1 in a sample from the subject wherein the determined expression level is used to provide a characterisation of and/or a prognosis for the cancer.

[0007] According to a further aspect of the invention there is provided a method for diagnosing (or identifying or characterizing) a cancer, such as prostate cancer or ER positive breast cancer, with an increased metastatic potential in a subject comprising:

[0008] determining the expression level of at least one gene from Table 1 in a sample from the subject wherein the determined expression level is used to identify whether a subject has a cancer, such as prostate cancer or ER positive breast cancer, with increased metastatic potential.

[0009] The invention also relates to a method for characterising and/or prognosing a cancer, such as prostate cancer or ER positive breast cancer in a subject comprising:

[0010] determining the expression level of at least one gene from Table 1 in a sample from the subject in order to identify the presence or absence of cells characteristic of an increased likelihood of recurrence and/or metastasis wherein the determined presence or absence of the cells is used to provide a characterisation of and/or a prognosis for the cancer, such as prostate cancer or ER positive breast cancer.

[0011] In a further aspect, the present invention relates to a method for characterising and/or prognosing a cancer, such as prostate cancer or ER positive breast cancer in a subject comprising:

[0012] a) obtaining a sample from the subject/in a sample obtained from the subject

[0013] b) applying a nucleic acid probe that specifically hybridizes with the nucleotide sequence of at least one gene or full sequence or target sequence selected from Table 1 to the sample from the subject

[0014] c) applying a detection agent that detects the nucleic acid probe-gene complex

[0015] d) using the detection agent to determine the level of the at least one gene or full sequence or target sequence

[0016] d) wherein the determined level of the at least one gene (or full sequence or target sequence) is used to provide a characterisation of and/or a prognosis for the cancer, such as prostate cancer or ER positive breast cancer. Suitable probes and probesets are listed in Table 1 and further details are provided in Table 1A.

[0017] In a further aspect, the present invention relates to a method for characterising and/or prognosing a cancer, such as prostate cancer or ER positive breast cancer in a subject comprising: